Tolerance to sedative drugs in PICU: Can it be moderated or is it immutable?

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Tolerance to sedative drugs in PICU: Can it be moderated or is it immutable?

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Nienke Vet and colleagues have evaluated the influence of daily sedation interruptions (DSI) in PICU. This was ambitious: bias is hard to avoid and recruitment rates in such studies are poor, which ultimately restrict the strength of conclusions. Nevertheless, their results suggest that if behavioral tools already drive sedation delivery, then DSI will not substantially influence the duration of ventilation. These findings are consistent with recent reports from adult intensive care (1).

A pause in drug delivery allows plasma concentration to fall followed by reduction in effect site concentration and subsequent arousal. However, the lag time can be significant (Figure 1a). Recovery may be further delayed by the presence and influence of midazolam's alpha-hydroxy metabolite that has half the activity of the parent drug (2). Other drugs used for sedation also have influence; a three-drug combination (e.g., midazolam, propofol, and alfentanil) can triple the duration of effect compared with propofol alone (3). In the current study additional sedative and analgesic drugs were used "as required". This may have contributed to the lack of impact from midazolam interruption. Variation in recovery from sedation is complicated by the high prevalence of renal failure, hepatic failure, and concomitant administration of CYP3A inhibitors in PICU patients. Sedation requirements vary widely not only with age, diagnosis and clinical state, but also between similar patients.

Sedation has parallels with innovations in postoperative pain control in children: intermittent drug use was replaced by continuous infusions, then patient and nurse controlled analgesia (PCA/NCA) with pain score monitoring. Further optimization combined low dose continuous infusions modulated by PCA/NCA. PICU sedation is in need of similar improvement but can this impact on patient outcomes? Practitioners of anaesthesia are also aware of emergence delirium complicating recovery. Could a

similar phenomenon complicate midazolam interruption, necessitating reintroduction of the drug prematurely?

The value of DSI (4,5,6) remains unclear. The results of this current study could simply reflect the strong history in the Netherlands of good sedation practice including a relative sparing use of sedatives. This is supported by the relatively low dose of midazolam used compared to a previous paediatric study (6). One conclusion is that recovery from sedation relates to the overall cumulative "sedation burden" and that minimizing the exposure with effective behavioral scoring linked to delivery, optimizes recovery irrespective of DSI and other factors.

Interventions such as those described by Vet and colleagues are complex. They consist of multiple linked elements: (7) context and setting (workload, resources, staffing); ICU staff characteristics (skill mix, training,) and clinical processes (complexity of proocols, algorithms, decision-making and perceived risk) (8). Understanding these components is critical to interpreting and generalizing study findings (9). This study does not provide contextual information that may help explain the results. An indication of the degree of compliance and nursing perspectives about the DSI may assist with interpreting the findings. Qualitative studies exploring non-adherence to DSI have highlighted a lack of nursing acceptance due to patient agitation and the subsequent risk of adverse events associated with more wakeful patients (11, 12). The UK Medical Research Council recommends that a process evaluation should accompany trials of complex interventions. (9).

Can tolerance be manipulated by modifying practice? Techniques that should be considered include: avoiding drugs particularly associated with tolerance such as midazolam, moderating early exposure to high doses of analgesics and sedatives to

prevent acute tolerance, drug-sparing strategies such as drug cycling or polypharmacy mixtures, and returning to low dose propofol, a drug that has been legislated out of PICU in many countries. Midazolam remains the most popular sedative despite association with withdrawal phenomena of up to 35% (13). The frequency and severity of tolerance and withdrawal is related to the cumulative "drug burden" and higher doses (≥300 mcg/kg/h) (14). A sedated patient is thought to be easier to nurse (15) and even in this current study children were sedated with mean midazolam doses (183-240 mcg/kg/h) to the deeper end of the sedation scale. There are alternatives to midazolam. Alpha-2 agonists can provide effective sedation either as a straight midazolam replacement or as a supporting drug (16,17). Currently there are no substantial data to determine if other drug combinations can reduce tolerance and accelerate recovery.

Acute exposure to high doses of high-efficacy short-acting opioids (e.g. fentanyl, remifentanil) is linked to accelerated drug tolerance (18) and delay in recovery. Fast track paediatric cardiac surgery has moved away from high doses fentanyl 100 mcg/kg or more to 10-15 mcg/kg over the perioperative period resulting in earlier extubation and accelerated recovery. There are potentially transferable lessons from this experience that could reduce tolerance in PICU patients. Drug delivery must reflect the age and context dependent pharmacokinetics. For example while drug delivery in the young infant needs to be high during the loading phase, downward adjustment is necessary during maintenance, reflecting reduced elimination compared to the older infant (Figure 1b). Unfortunately, behavioral scoring may be impossible in this early phase if neuromuscular blocking drugs are used, and higher doses than necessary may be continued. Rotating drug sedation and analgesic regimens, or using non-pharmacological strategies to maintain comfort have been used to try to limit drug requirements. While this approach makes sense there are no data to support it.

The SLEEPs trial (16) demonstrated that neither morphine/midazolam nor morphine/clonidine alone could always provide complete sedation. A third agent was often required. The choice of the third agent may be important: in the current study multiple rescue drugs were used. While propofol as a major sedative agent has been eliminated from use in PICU due to fears of propofol infusion syndrome, it continues to be used cautiously by some, even in countries where the drug is officially discouraged. Low-dose infusion (0-4 mg/kg/h) with careful surveillance for accumulation and lactic acidosis deserves to be reconsidered as a third-line drug.

Sedation is often treated as a necessary evil in PICU: the primary disease and its treatment is naturally the main focus while sedation is managed generically. During recovery the secondary problems associated with sedation (e.g., nosocomial infection, poor gut motility and behavioral change) become lost within the disease and general PICU experience. Under-sedation and over-sedation are both harmful: minimizing sedation exposure and their adverse effects are important. Optimized matching of delivery to sedation requirement provides another marginal gain in the critically ill child that can contribute to improving patient outcomes.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Figure 1a. Plasma concentrations and effect in a 2-year-old child given protocol midazolam bolus (0.1 mg/kg) and infusion changes (100 mcg/kg/h step changes) every 30 min to achieve sedation. Infusion was stopped at 180 min. Sedation recovery lags behind the decline in plasma concentration. Amplitudes in the 11.5-30 Hz (beta) frequency band were used as an EEG effect measure. Pharmacodynamic parameter estimates were from Mandema J et al. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteer. Clin Pharm Ther 1992;51:715-28

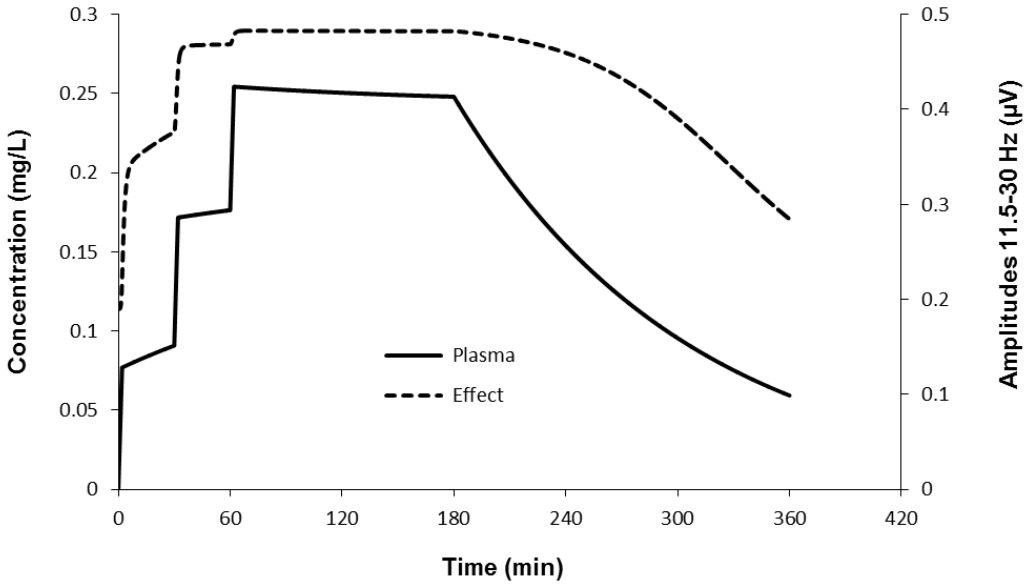
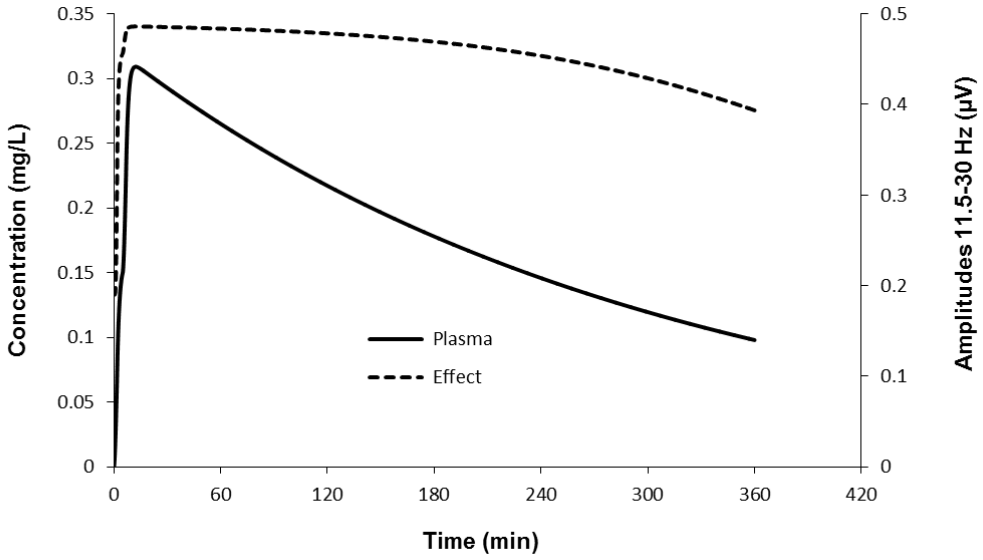


Figure 1b. Plasma concentrations and effect in a neonate given protocol midazolam bolus (0.1 mg/kg) on two early occasions (5 min interval) to achieve sedation. Plasma concentration declines slowly because of slow clearance. Sedation recovery lags way behind the decline in plasma concentration even though a maintenance infusion was not even given. Pharmacodynamic parameter estimates were from Mandema J et al. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteer. Clin Pharm Ther 1992;51:715-28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